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Findings From the U.S. Navy-Marine Corps Combat
Trauma Registry***

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**Use of Recombinant Factor VIIa for Control of Combat-Related Hemorrhage:
Findings From the U.S. Navy-Marine Corps Combat Trauma Registry**

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Abstract

New methods of hemorrhage control are needed for use in remote surgical locations, such as the battlefield. Data from the Navy-Marine Corps Combat Trauma Registry (CTR) describe recombinant activated human coagulation factor VII (FVIIa), a site-specific, intravascular approach to promote clotting, which is being used as an adjunct to surgical control of bleeding in trauma patients in the battlefield environment. The present 20-month retrospective study identified 22 casualties from the CTR who were wounded in Iraq and received FVIIa. Primarily young Marines, these patients typically had penetrating injuries from improvised explosive devices and gunshot wounds. Injuries were often abdominal, supporting the utility of FVIIa for noncompressible injuries. The average dose used was similar to that reported elsewhere, although dosing varies widely in the existing experimental and anecdotal literature. Over two thirds (68%) of the FVIIa patients survived. Survival outcomes did not differ significantly between the FVIIa group and a matched “control” group. Results are discussed in terms of battlefield applications for FVIIa and methodological limitations of the study.

Blood loss is a major cause of death among combat casualties in the battlefield (Bellamy, 1984; LSRO, 2005). Conventional damage-control treatments, such as transfusion, may be unsuccessful. Although hemorrhage is responsible for a large number of combat deaths, published coagulation studies with combat patients are limited. Because of the challenges of treating hemorrhage during combat, it is important for military medical personnel to understand their options for treating hemorrhage quickly and efficiently.

Recombinant activated human coagulation factor VII (FVIIa) is a serine protease that was originally developed for use in hemophiliacs with inhibitors (Hedner & Erhardtsen, 2002). Because of its procoagulant properties, its use has been expanded to other types of patients to overcome a variety of coagulation and platelet disorders. For example, it has been used with trauma patients with massive hemorrhage and coagulation problems. Controlled animal trials, small case studies, and anecdotal reports suggest that FVIIa may slow down and even control massive bleeding in trauma, and hence prolong survival and reduce mortality (Holcomb, 2005). FVIIa is now being used in major trauma centers throughout the world on a compassionate-need basis.

Animal studies and civilian efficacy and safety data suggest that “fielding” of FVIIa to the combat setting may widen the survival window of hemorrhaging casualties. FVIIa promotes coagulation only at the site of the traumatic injury, and has other advantages that lend themselves to battlefield trauma, such as a rapid onset, short half-life (Hedner & Erhardtsen, 2002), and ease of administration (Sapsford, 2004). However, there are potential drawbacks to using FVIIa that should be considered, including

complications such as unwanted thrombosis (O'Connell, Wood, Wise, Lozier, & Braun, 2006), and the expense of FVIIa.

Controlled trials of the effectiveness of FVIIa in the combat setting are unlikely; therefore, assessments of FVIIa in this environment will likely be based on observational and descriptive data. Physicians have been using FVIIa at on-the-ground surgical units in Iraq on a compassionate-use basis typically as an injectible adjunct to standard hemostatic maneuvers (Holcomb, 2005). However, there is little information about the clinical characteristics and outcome of combat casualties who receive FVIIa. The purpose of the present study was to present available data from the Navy-Marine Corps Combat Trauma Registry (CTR) to describe the initial experiences with FVIIa at far-forward Navy-Marine Corps medical treatment facilities (MTFs). Clinical features and disposition of FVIIa patients are presented. In addition, a comparison group composed of casualties from the registry for the same time period who did not receive FVIIa were used to estimate the benefit of FVIIa on clinical outcomes.

Methods

Data for the present study came from the CTR, a deployment health database comprising trauma data captured from (a) Levels 1 and 2 Navy and Marine Corps MTFs, and (b) the Joint Theater Trauma Registry. In addition, the CTR contains nonbattle injury data, disease data, psychiatric data, and routine day-to-day sick-call encounters (for a more-detailed description, see Galarneau et al., 2006).

One purpose of the CTR is to analyze combat injury patterns (particularly near the point of injury) and inform casualty management for wounded personnel throughout the medical chain of evacuation. Medical encounter forms are completed either on paper or

electronically by health care providers at Navy-Marine Corps MTFs in theater, and forwarded to CTR staff at the Naval Health Research Center (NHRC), in San Diego, CA, on an ongoing basis.

Medical encounter data from the CTR were reviewed to identify all battle-injured patients documented as having received FVIIa during the period May 2004 to January 2006. CTR clinical staff at NHRC read narrative fields from the encounter form that were written by the provider in theater and, in the case of evacuated patients, from clinical records completed at subsequent levels of care (i.e., Army Level 3 MTFs and Landstuhl Regional Medical Center). The narrative fields typically describe the injury, the circumstances surrounding the injury, treatment strategies, and response to treatment. Inclusion criteria for the study included any mention of the use of FVIIa in a narrative field, and one or more of the following: (a) hypotensive from blood loss, (b) a base deficit greater than 6, (c) coagulopathic bleeding or an international normalized ratio greater than 1.5, (d) need for damage control maneuvers, (e) need for fresh whole blood, (f) anticipated and actual transfusion of greater than 4 units of packed red blood cells, (g) difficult-to-control bleeding associated with hypothermia ($<96^{\circ}\text{F}$), and (h) anticipated significant operative hemorrhage. Those patients suffering a head/brain trauma *exclusively* were excluded from the study.

The following clinical data were abstracted from each patient's medical record beginning with the encounter form: age at time of injury; mechanism of injury; anatomical location of primary injury; Injury Severity Score (ISS), an overall measure of severity, with scores ranging from 0 to 75 (Baker, O'Neil, Haddon, & Long, 1974; Baker & O'Neil, 1976); FVIIa dose; blood product utilization near the time of FVIIa

administration; whether bleeding was stemmed as a result of *any* treatment (yes or no); and whether the patient survived longer than 48 hours (yes or no).

Clinical staff identified 22 contemporaneous control subjects from the CTR who were coagulopathic patients but who did not receive FVIIa. Controls were matched to FVIIa cases based on ISS and age. A check of the matching procedure showed that the two treatment groups did not differ significantly by ISS, age, anatomical location of primary injury, or mechanism of injury.

Results

Twenty-two cases, all male, were identified as having received FVIIa during the period of interest. Patients averaged 24 years of age (range, 19-32). Fifteen patients were Marines, 5 were Army personnel, 1 was a Navy service member, and the service of 1 patient was unknown. About half received FVIIa at a forward MTF (i.e., Level 2), and half at an Army Level 3 facility.

Table 1 presents characteristics of the 22 casualties. Improvised explosive devices (IEDs) and gunshot wounds were the two most common mechanisms of injury (41% and 32%, respectively). Most patients were suffering from multiple anatomical site injuries at the time of FVIIa administration. The anatomical region of the single most significant injury was the abdomen (55%), followed by injury to an extremity (27%). All but 3 patients received a penetrating wound (versus blunt force trauma) as their primary injury. The median ISS was 24.

Table 1. Description of Patients Receiving FVIIa for Control of Bleeding

Patient Number	Age	Mechanism of Injury	Site of Primary Injury	ISS	Bleeding Stemmed	Survived
1	27	IED	extremity	34	Yes	Yes
2	19	Rocket	pelvis	9	Yes	Yes
3	23	Mine	extremity	10	Yes	Yes
4	24	RPG	extremity	45	Yes	No
5	21	IED	abdomen	29	No	Yes
6	26	IED	extremity	9	Yes	Yes
7	22	GSW	abdomen	32	Yes	Yes
8	21	GSW	abdomen	41	Yes	No
9	Unk	Mortar	abdomen	18	Yes	Yes
10	21	GSW	flank	25	Yes	Yes
11	Unk	IED	abdomen	17	No	Yes
12	30	IED	flank	18	Yes	Yes
13	29	GSW	abdomen	Unk	Unk	No
14	23	IED	abdomen	32	Yes	No
15	22	Mortar	abdomen	22	Yes	Yes
16	32	IED	extremity	21	No	Yes
17	23	Mortar	abdomen	34	Yes	Yes
18	24	IED	abdomen	29	Yes	Yes
19	Unk	GSW	head	Unk	No	No
20	Unk	GSW	abdomen	26	Unk	No
21	32	GSW	abdomen	25	No	No
22	31	IED	extremity	10	Yes	Yes

Note. GSW = gunshot wound; IED = improvised explosive device; ISS = Injury Severity Score; RPG = rocket propelled grenade; Unk = Unknown.

Although details were incomplete, clinical records indicated that two thirds of patients had a Class 4 hemorrhage (the most severe blood loss according to the American College of Surgeons classification), and almost all were documented as being in shock. Around the time of administering FVIIa, patients received, on average, 14 units of packed red blood cells, and 8 units of fresh frozen plasma (information from clinical records was too incomplete to estimate the amount of whole blood, platelets, and cryoprecipitate). Patients averaged two doses (median) of FVIIa, for a total average of 9.6 mg/kg.

Of the 22 patients who might have died from exsanguination, 15 (68%) survived for longer than 48 hours. This survival rate was *identical* to that of the control patients,

$\chi^2(1) = 0.00, p = 1.00$. Cessation of bleeding was higher in the control group (100%) than in the FVIIa group (75%), although the difference did not reach statistical significance, $\chi^2(1) = 3.56, p = .06$.

Discussion

FVIIa has mostly been used in civilian trauma centers as a last-resort strategy after conventional treatments, such as large-volume resuscitation, transfusion, and damage control procedures, have been tried (Holcomb, 2005). Numerous anecdotal reports (Dutton, et al., 2004; Martinowitz, Kenet, Segal, & Lubetsky, 2001; O'Neill, et al., 2002) and animal models (Jeroukhimov, et al., 2002; Lynn, et al., 2002; Martinowitz, Holcomb, & Pusateri, 2001; Schreiber, et al., 2002) have generally supported the potential benefit of FVIIa to treat uncontrolled bleeding, and recent randomized trials indicated a trend toward higher survival among civilian trauma patients receiving FVIIa compared with standard care controls (Boffard, et al., 2005).

Despite growing evidence from studies with civilian trauma patients, little is known about the circumstances and outcomes of the use of FVIIa for *combat-related* trauma. The present 20-month retrospective study identified 22 casualties from the Navy-Marine Corps CTR who were wounded in Iraq, and who received FVIIa. Primarily young Marines, these patients typically had penetrating injuries from IEDs and gunshot wounds. Injuries were often abdominal, supporting the utility of FVIIa for noncompressible injuries. The average FVIIa dose used was similar to that reported elsewhere (Benharash, Bongard, & Putnam, 2005), although dosing varies widely in the existing experimental and anecdotal literature. Over two thirds (68%) of the FVIIa patients survived, a notable

percentage given that severely injured civilian trauma patients have up to a 50% mortality rate (Rotondo & Zonies, 1997; Shapiro, Jenkins, Schwab, & Rotondo, 2000).

We found no differences in survival outcomes between the FVIIa group and a “control” group matched for ISS and age. While several studies have documented the benefits of FVIIa in trauma patients, the results are somewhat mixed. For example, Dutton and colleagues (2004) found a *higher* mortality among FVIIa patients than among matched coagulopathic controls. There may be a number of reasons why we did not find differences in clinical outcomes between FVIIa patients and controls in the present study. One possibility is that there is no advantage to using FVIIa. Another possibility is that the two groups were not matched on a missing critical variable (e.g., serum lactate). The availability of FVIIa and protocols for administering it in the combat setting are not known to us; in fact, FVIIa use, timing, and dosages may occur on a nonstandard, case-by-case basis. It may be that FVIIa was not used until conventional therapies had failed. Therefore, those receiving FVIIa may have had a worse response-to-treatment history than controls, rendering the two groups nonequivalent (this point is somewhat supported by the better bleeding control outcome of the control group relative to the FVIIa group). As Dutton and colleagues (2004) pointed out, the use of FVIIa as a therapy of last resort makes the identification of an appropriate control group difficult. Assuming FVIIa patients indeed had a worse response-to-treatment profile than their control counterparts, their identical survival rate is noteworthy, and may be an indication of the effectiveness of FVIIa. Clearly, this small descriptive study is not designed to formally test the efficacy of FVIIa, and results are inconclusive.

Coagulation parameters (e.g., prothombin time, partial thromboplastin time, international normalized ratio) were not available from the clinical records to assess patients' hemostatic response to FVIIa. These parameters, ideally collected both before *and* after administration of FVIIa, would have been useful as a measure of FVIIa effectiveness. The CTR is one of the first successful attempts to collect trauma data from the combat theater so close to the time of injury. However, getting a complete clinical description of injured patients (particularly those injured in battle), is a formidable task, and records are often only partially completed.

New methods of hemorrhage control are needed for use in remote surgical locations, such as the battlefield. CTR data show that FVIIa, a site-specific, intravascular approach to promote clotting, is being used as an adjunct to surgical control of bleeding in trauma patients in the battlefield environment. The majority of patients receiving FVIIa survived, a positive finding given that patients were in extremis. Our data did not show FVIIa to be superior to standard care, although methodological difficulties and our small sample size preclude drawing conclusions about the relative effectiveness of FVIIa. Additional combat studies with more-complete clinical data and a larger sample are needed to evaluate the impact of FVIIa, and the conditions under which it is most effective.

The military surgeon has limited resources and the potential for being overwhelmed by many casualties, and as a result, FVIIa may make an important contribution to combat casualty care (Sapsford, 2004). FVIIa may have a damage control role, quickly arresting blood loss until the casualty can be evacuated to a higher-echelon hospital for more definitive care. Potentially, FVIIa could even be administered

immediately after the injury by first line medics/corpsmen, prolonging survival until surgical control of bleeding can be conducted. However, reports of unusually high rates of unwanted clots among civilians (O'Connell et al., 2006) and military personnel (Gawande, 2004) treated with FVIIa suggest that controlled studies are needed to establish the safety and efficacy of FVIIa for trauma patients.

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